Optimizing Depression Treatment: Clinical and Economic Benefits of Early Repetitive Transcranial Magnetic Stimulation

This statement is in support of the use of repetitive transcranial magnetic stimulation (rTMS) early in the treatment algorithm for major depressive disorder (MDD).The initial Food and Drug Administration (FDA) clearance of TMS was granted for those who had failed to achieve satisfactory response to one trial of antidepressant ("510(k) Premarket Notification," n.d.) after the initial clinical trials showed efficacy of rTMS over placebo in patients who had tried 1-4 antidepressant trials (George et al. 2010; O'Reardon et al. 2007; Levkovitz et al. 2015). Despite this, many insurance provider policies *require* patients to demonstrate 2-4 failed medication trials and therapy before meeting medical necessity criteria for rTMS treatment coverage. These requirements of demonstrating a high degree of medication resistance are not supported by clinical evidence and delay access to effective treatment leading to worsening depressive symptoms, impaired quality of life, difficulty managing daily activities, increased risk of suicidal behaviors, and negative impacts on relationships and work productivity. Furthermore, prolonging a depressive episode may make it harder to treat effectively reducing the likelihood of full remission (Oluboka et al. 2017).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that approximately 30% of patients fail to achieve remission after two medication trials (Rush et al. 2006). Moreover, with each additional medication trial or medication augmentation strategy, the likelihood of remission declines significantly, and depression recurrence increases, highlighting the challenge and risk of treatment resistance when relying heavily on pharmacotherapy and behavioral therapy alone. Given this high risk, medication-resistant depression places a substantial burden not only on individuals—contributing to prolonged suffering and functional impairment—but also on society, driving increased healthcare costs (Bangalore et al. 2020), lost productivity (Jaffe, Rive, and Denee 2019), and economic strain (Heerlein et al. 2022). Thus, offering alternative treatment options, such as rTMS, sooner in depression management should be considered to improve outcomes and economic burdens of untreated depression.

There is significant clinical evidence that rTMS should be used earlier in the depression treatment algorithm. rTMS is more effective in people with less treatment resistance and shorter duration of depressive episode (Brakemeier et al. 2007). Recently, a multi-site head-to head randomized clinical trial in 89 patients was conducted comparing depression outcomes in patients who had failed at least 2 antidepressants and had utilized psychotherapy. Patients were randomized to another medication trial or rTMS. The rTMS group demonstrated a larger decrease in MDD symptoms scores than the medication group with a large effect size (Cohen's d= 0.77) (Dalhuisen et al. 2024). A separate multi-site study of 260 patients randomized to augmentation with aripiprazole or rTMS versus switching to the antidepressant venlafaxine XR or duloxetine. This study also showed that rTMS was superior to switching medications in patients who had failed at least two medication trials (Papakostas et al. 2024). In this study, the

rTMS group had a 4.17 greater mean reduction in the Montgomery-Asberg Depression Rating (MADRS) assessment compared to the medication switch group demonstrating that rTMS should be considered in patients who have demonstrated medication non-response earlier in the management strategy of depressed patients.

Using rTMS soon after the onset of a depressive episode in the depression treatment pathway offers not only clinical benefits but also cost-effectiveness. A study comparing rTMS to the next medication trial in patients who had already failed two antidepressants found that, over the following 12 months, the rTMS group had higher response and remission rates, greater Quality-Adjusted Life Years (QALYs), and lower overall costs than the medication group (Dalhuisen et al. 2024.). To determine overall costs, the study measured intervention costs (rTMS and psychotherapy), healthcare utilization (medical consultations and medication use), informal care (support from family/friends and transportation), and productivity losses (missed work and reduced efficiency). Although the initial intervention costs were higher for the rTMS group, the medication group had consistently higher healthcare costs and productivity losses at both 6 and 12 months. As a result, the total costs were greater for the medication group, demonstrating that rTMS is a cost-effective alternative to additional antidepressant trials, with favorable incremental cost-utility ratios and cost-effectiveness acceptability curves.

Together the evidence supports rTMS use early in the treatment algorithm leads to better treatment outcomes and economical care. It is the position of the Clinical TMS Society that TMS should be promoted in adherence with the initial FDA clearance and rTMS should be offered to patients after one antidepressant trial that does not result in remission of the depressive episode.

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